



## State-of-the-molecules

## RESVERATROL: A CROSSROAD OF ENOLOGY AND BIOMEDICINE

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*Interest in the potential health benefits of resveratrol, a constituent of red wine, has increased significantly in the past decade. Extensive research has been done on it in attempt to reveal its clinical potential both in terms of disease prevention and treatment. Since initially resveratrol has been regarded as an explanation for the French paradox, attention of health professionals and journalists has been drawn to it. Called “promising molecule”, “star molecule” or “wonder drug”, resveratrol has been reposed hope as a cardioprotective, neuroprotective, anticancer, antiinflammatory, and antiaging molecule. Here we present state-of-the-resveratrol elucidating its role in promotion of health and prevention of disease. **Biomed Rev 2007; 18: 89-101.***

**Key words:** anticancer, antiinflammatory, apoptosis, cardioprotective, longevity, neuroprotective, red wine, hormesis

*“Quickly, bring me a beaker of wine, so that I may wet my mind and say something clever.”*  
**Aristophanes**, ancient Greek comedy writer, 450-385 BC

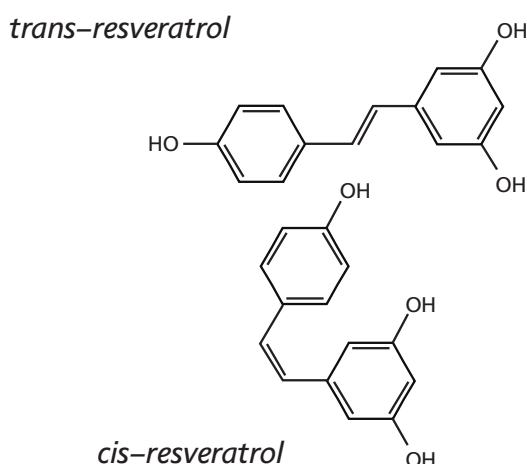
**INTRODUCTION*****Structure and synthesis***

Resveratrol (RSV) is a non-flavonoid polyphenol/phytoalexin, 3,5,4'-trihydroxystilbene, a member of the viniferin family of polymers. It is a fat-soluble compound that exists in *trans*- and *cis*- configuration. The *trans* isomer is more active. It converts to *cis* form when exposed to UV irradiation. Both *cis*- and

*trans*-RSV (Fig. 1) also occur as glucosides. The 3- $\beta$ -glucoside of RSV is called piceid and is also biologically active (1). The synthesis of RSV from *p*-coumaroyl CoA and malonyl CoA in some plants is induced by stress, injury, fungal infection, or UV irradiation. The key enzyme is stilbene synthase (RSV synthase).

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**Figure 1.** Structure of resveratrol.

## DISCOVERY AND ISOLATION

Now RSV is known as a compound of the grape skins and has been found in high concentration in red wines, but in 1963 in Japan Nonomura *et al* isolated it from the roots of the plant *Polygonum cuspidatum* (2). Japanese enjoyed for centuries the Itadori tea as a herbal remedy for heart disease and stroke (3). Nowadays the plant known as Japanese knotweed or Ko-jokon in Japan and Huzhang in China, nevertheless considered an aggressive and noxious weed in Europe and America, is the most widely used and cheapest source of RSV for dietary supplements.

Resveratrol was isolated by Takaoka in 1939 from the roots of the white hellebore (*Veratrum grandiflorum*) (4). The name was most probably derived in the following way (5): **res**: might be an abbreviation of the class of molecules: RSV belongs to the resorcinols; **veratr**: abbreviation of the plant name, *Veratrum*; **ol**: is generally used for indicating hydroxyl groups. In 1976 RSV has been characterized as phytoalexin, a substance synthesized by leaf tissue in response to fungal infection of grapevines (6). The fungus *Botrytis cinerea* (gray mold) induces RSV synthesis in healthy plants and the content of RSV in grapes determines the natural fungal resistance (7). This mechanism of defense has only been adopted by few plant species because most lack the key enzyme (8). The generally favorable biological responses to low exposure to stress are called (xeno)hormesis (see below).

In 1992 Creasy (9) analyzed different red wines for their RSV content and identified *trans*-RSV as biologically active compound. He linked *trans*-RSV to the reduction of serum lipids and explained in this way some of the cardioprotective effects of red wine.

## SOURCES

Resveratrol is found in over 70 plant species including nuts, grapes, pine trees, certain vines and red wine (10). Generally, white wines contain 1–5% of the RSV content present in most red wines. Resveratrol's most frequent plant sources are: root and rhizome of *Polygonum cuspidatum* (*Fallopia Japonica*); red grapes (skins, seeds, stalks, roots) of the *Vitaceae* family vines, species *Vitis vinifera* (the European winemaking grapes), *Vitis labrusca* (the North American grapes) and *Vitis rotundifolia*, the muscadines (native grape grown of the south-eastern USA), i.e. grape juice, must, pulp, pomace (the mass of grape skins, seeds and stems left after fermentation), wine; peanuts and pistachios; berries: blueberry, cranberry, mulberry, deerberry, bilberry, lingonberry, sparkleberry, partridgeberry, and jackfruit; trees: pines (Scots pine, eastern white pine), eucalyptus, spruce; flowers: white hellebore (veratrum); recently found in dark chocolate and cocoa (11).

The amount of RSV in wines varies according to the cultivar, its geographic origin, its growing conditions, and exposure to triggers of its production. The amount of time a wine spends in contact with skins and pulp during fermentation is an important determinant of its RSV content. As white wines are not fermented on their skins, they have a very low amount of RSV, regardless some white grapes also produce it. Muscadine wines are more resistant to pests and diseases, including *Phylloxera*, an insect that almost wiped out the European vineyards and devastated most of the European wine growing industry in the late 1800s; they have the highest content of RSV (12–14) (Table 1).

**Table 1.** Resveratrol content in wines and grape juice

Beverage	Total resveratrol (mg/L)	Total resveratrol (mg) in a 5 ounce (150 ml) glass
Muscadine wines	14.1 – 40	2.12 – 6
Red wines	1.98 – 7.13	0.30 – 1.07
Red wines (Spanish)	1.92 – 12.59	0.29 – 1.89
Red grape juice (Spanish)	1.14 – 8.69	0.17 – 1.30
Rose wines (Spanish)	0.43 – 3.52	0.06 – 0.53
Pinot Noir	0.40 – 13.4	0.06 – 2.01
White wines (Spanish)	0.05 – 1.80	0.01 – 0.27

### ABSORPTION AND BIOAVAILABILITY

Resveratrol has a good absorption of about 70% when given orally and intravenously, but has low bioavailability because it is rapidly metabolized and eliminated. The metabolites of RSV are resveratrol-3-sulphate, resveratrol-3-O-glucuronide and dihydroresveratrol. RSV has a plasma half-life of  $9.2 \pm 0.6$  h. After absorption only traces of the unchanged RSV are found in plasma (15). In another *in vivo* study *trans*-RSV were found only in some serum samples collected 30 min. after red wine ingestion while glucuronides predominated. *Trans*-RSV bioavailability was shown to be independent from the meal or its lipid content (16). The bioavailability of RSV from grape juice, which contains mostly RSV glucosides (piceid) may be even lower than that of *trans*-RSV, because the glycoside forms are absorbed to a lesser extent (17).

### ANTIOXIDANT ACTIVITY OF RESVERATROL

Resveratrol is an effective antioxidant *in vitro*. It scavenges reactive oxygen species (ROS) including oxygen ions, free radicals, and peroxides involved in oxidative stress (18-20). In some studies *trans*-RSV was found to be a better radical scavenger than vitamins E and C (18) but in others it was less potent than ascorbic acid (21). Resveratrol protects against and inhibits low-density lipoprotein (LDL) oxidation (22,23).

Resveratrol is a potent antioxidant *in vivo*. This property is probably a result of its ability to increase nitric oxide (NO) synthesis, which in turn functions as an *in vivo* antioxidant, scavenging superoxide radicals. Resveratrol (i) induces NO synthesis and lowers oxidative stress in the ischemic reperfused heart, brain, and kidney (24,25), (ii) manifests antioxidant activity in different cell culture lines, including cancer cell lines, (iii) inhibits proliferation that had been accompanied by a reduction in NO production or by an inhibition of inducible NO synthase (iNOS) (26,27), and (iv) maintains the concentrations of intracellular antioxidants like glutathione (GSH) (28) and increase the amounts of several antioxidant enzymes, including glutathione peroxidase, glutathione-S-transferase and glutathione reductase (29). The nuclear factor-kappa B (NF-k-B) signaling pathway can be evoked by oxidative stress and is inhibited by RSV (21). Tumor necrosis factor-alpha (TNF- $\alpha$ )-induced activation of NF-k-B is attenuated by RSV (30). RSV inhibits angiotensin-II (AT-II)-induced cardiomyocyte hypertrophy by inhibiting the AT-II-induced ROS production (31).

### CARDIOPROTECTIVE ACTIVITY

The French paradox, a very low mortality rate due to coronary heart disease (CHD) in France despite a high-saturated-fat diet and smoking habits (32), was first noted as a phenomenon by the Irish physician Samuel Black in 1819, described in 1958 by British authors (33) and ascribed to red wine consumption in 1992 (34). Despite its validity has been questioned and other theories have been proposed to explain the paradox – under-reporting or peculiarities of reporting CHD mortality in France, time lag explanation, pattern of drinking, the diet-heart hypothesis etc. (35,36), the scientific interest in red wine remained high. Numerous studies established that moderate alcohol consumption is beneficial and has a J-shaped mortality curve. Clear proof for decreased total mortality associated with 2-4 daily drinks for men and 1-2 for women *versus* abstinence or higher drinking rates came from a meta-analysis of mortality in 34 outcome studies on more than 1 million subjects with nearly 100 000 deaths analysed (37,38). Moderate wine drinkers had a 32% average decreased risk of cardiovascular disease compared to non-drinkers, and beer drinkers had less benefit. But is it alcohol, wine, red wine (39) or some red wine compounds? Resveratrol is one of wine constituents mostly believed to be responsible for this phenomenon. Whatever, "wine makes heart happy" (from Greek, *oinos euphrainei cardian*).

**1 standard drink is** 12 grams of alcohol, equivalent to one 12-ounce (360 ml) can or bottle of 4% beer or 6 oz (120 ml) of 8% beer, one 5-ounce (150 ml) glass of wine, or 1.5 ounces (45 ml) of 40% alcohol distilled spirits.  
[1 fluid ounce = 30 ml]

### Platelet aggregation

Resveratrol inhibits platelet aggregation *in vitro* and *in vivo* (40,41). This effect of RSV could be explained by its preferential inhibition of cyclooxygenase 1 (COX1) over COX2. In this way the activity of prostacyclin, a vasodilator and antiplatelet aggregator, synthesized by COX1 in platelets, prevails over thromboxane A2, a potent vasoconstrictor and inducer of platelet aggregation, synthesized by COX2. Resveratrol may cause irreversible inactivation of COX1 under some conditions (42) thus having a lasting effect even after a short exposure *in vivo*.

### ***Vasorelaxation***

Resveratrol exerts additional vasorelaxant effect on isolated porcine coronary arteries (43). As a possible mechanism for this was proposed its ability to stimulate  $\text{Ca}^{2+}$ -activated  $\text{K}^{+}$  channels in endothelial cells (44) and to lead to decreased NO inactivation through inhibition of vascular NADH/NADPH oxidase activity (45). *In vivo* RSV leads to a coordinated upregulation of both iNOS and endothelial NO synthase (eNOS) (46,47), whereas fails to provide cardioprotection in iNOS knockout mice (48), but it reduces myocardial ischemia reperfusion injury through both iNOS-dependent and iNOS-independent mechanisms (49).

### ***Anti-inflammatory effects***

The cardioprotective ability of RSV is also due to its anti-inflammatory effects in the ischemic heart. Possible mechanisms for its protective activities include the inhibition of synthesis and release of pro-inflammatory mediators, modifications of eicosanoid synthesis, inhibition of activated immune cells, the enzymes COX1 and COX2, and transcription factors such as NF $\kappa$ B and activator protein-1 (AP-1) (50). Resveratrol inhibits the expression of adhesion molecules including intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in cultured endothelial cells (51,52). Intravenously administered RSV decreases inflammation induced by ischaemia/reperfusion in rats (53). Moderate hyperhomocysteinemia is an independent risk factor for cardiovascular disease and RSV has been found to suppress homocysteine formation in stimulated human peripheral blood mononuclear cells *in vitro* (54).

### ***Anti-apoptosis***

Resveratrol is capable of inducing anti-apoptotic signaling, and thereby ensuring heart protection. In porcine coronary arteries, short term treatment with RSV significantly inhibited mitogen-activated protein kinase (MAPK) activities, and immunoblot analyses revealed consistent reduction in the phosphorylation of extracellular signal-regulated kinases 1/2 (ERK1/2), Jun N-terminal kinase (JNK-1), and p38 MAPK (55). The same study found that RSV attenuated basal and endothelin 1-mediated protein tyrosine phosphorylation. Evidence for the anti-apoptotic function of RSV is further found in other studies, which have demonstrated a reduction of apoptotic cardiomyocytes in the ischemic reperfused heart that had been pretreated with RSV (48). Resveratrol, but also other wine compounds like proanthocyanidin, acts as a strong

antioxidant and triggered a signal transduction cascade by reducing proapoptotic transcription factors and genes such as JNK-1 and c-Jun thereby potentiating an anti-death signal. This resulted in the reduction of myocardial infarct size and cardiomyocyte apoptosis in isolated rat hearts (56). However, RSV has been found to inhibit proliferation and to have a pro-apoptotic effect in different cancer cell lines (57, also see below).

### ***Pharmacological preconditioning***

Preconditioning is the most powerful "technology" known to make the heart resistant to subsequent lethal ischemic injury. Most often preconditioning is performed by 4 cycles of ischemia (5 minutes each) followed by 10 minutes of reperfusion (58). The intracellular signaling mechanisms are second messenger pathways that involve components such as adenosine, adenosine receptors, NO, heat shock proteins (Hsp), protein kinase C, the mitochondrial ATP-dependent potassium channels, including a paradoxical protective role of oxygen free radicals (59). Recently it was determined that RSV may function as a pharmacological preconditioning agent. It improves postischemic ventricular functional recovery, reduces myocardial infarct size and also cardiomyocyte apoptosis. Additionally, RSV diminishes the amount of ROS activity, which was demonstrated through reduced malonaldehyde formation. Also, RSV exerts its preconditioning effect through NO (24). In normal tissue, RSV decreases the expression of iNOS, however in ischemic heart RSV induces iNOS. iNOS knockout mouse hearts could not be preconditioned with RSV in contrast to wild type mouse hearts (48). Resveratrol protects the ischemic heart through the increased expression of adenosine A1 and A3 receptors (60).

### ***Angiogenic properties***

Therapeutic angiogenesis is the clinical use of methods to enhance or promote the development of collateral blood vessels and thus improving blood flow to ischemic tissue. The neovascularization is induced by angiogenic agents administered as recombinant protein or by gene therapy. In the past decade the method has been applied in patients with coronary artery disease and peripheral artery disease. There are three major ways to promote angiogenesis: protein therapy (by vascular endothelial growth factor – VEGF, basic fibroblast growth factor - bFGF), gene therapy, and cell therapy (61). Three weeks after infarction, RSV treatment leads to increased expression of VEGF/Flk-1 receptor (62) and eNOS and iNOS (46).



## NEUROPROTECTIVE EFFECTS

The results of several studies indicate the usefulness of RSV in protecting against brain damage following focal or global cerebral ischaemia in rodents (63-65). Resveratrol is able to prevent seizures induced by kainic acid, FeCl<sub>3</sub> or pentylene-tetrazole (66-68). Chronic treatment with RSV counteracts in part streptozotocin-induced cognitive impairment (69). Recent data showed that RSV might also have a therapeutic potential in Alzheimer's disease. Resveratrol markedly lowers the levels of secreted and intracellular amyloid- $\beta$  (A $\beta$ ) peptides produced from different cell lines. It does not inhibit A $\beta$  production, but promotes instead intracellular degradation of A $\beta$  via a mechanism that involves the proteasome (70). Resveratrol is found to be neuroprotective in several models of Huntington's disease (HD) - a nematode model and neuronal cell culture derived from a genetic HD mouse (HDhQ111 knock-in mice) (71), toxin mouse model of HD (72). Resveratrol appears to be beneficial in a mouse model of amyotrophic lateral sclerosis (73).

## ANTICANCER EFFECTS

In 1997 Jang *et al* reported that topical application of RSV has cancer chemopreventive activity in assays representing three major stages of carcinogenesis (74). Since then extensive research on RSV's anticancer activities has been done. In some studies RSV was efficient in low doses if administered systemically (75) what suggests that it might possess therapeutic potential in concentration obtained from dietary sources, such as red wine. In other studies higher but pharmacologically achievable doses have been used. RSV has the ability to suppress proliferation of a wide variety of tumor cells, including lymphoid and myeloid cancers; multiple myeloma; cancers of the breast, prostate, stomach, colon, pancreas, and thyroid; melanoma; head and neck squamous cell carcinoma; ovarian carcinoma; and cervical carcinoma (57). Numerous pre-clinical studies demonstrated the potential chemopreventive and chemotherapeutic activities of RSV on all three stages of carcinogenesis (initiation, promotion, and progression), in both chemically and UVB-induced skin carcinogenesis in mice, as well as in various murine models of human cancers (76). There are various mechanisms via which RSV exerts its anticancer effects (see below).

### *Cell-cycle arrest and proapoptosis*

Resveratrol induces cell cycle arrest in different cell phases by upregulation of p21Cip1/WAF1, p53, and Bax; down-

regulation of survivin, cyclin D1, cyclin E, Bcl-2, Bcl-xL, and cIAPs; and activation of caspases (57). Resveratrol has been shown to suppress the activation of several transcription factors, including NF- $\kappa$ B, AP-1, and Egr-1; to inhibit protein kinases including I $\kappa$ B-kinase, JNK, MAPK, Akt, PKC, PKD, and casein kinase II; and to down-regulate products of genes such as COX-2, 5-LOX, VEGF, IL-1, IL-6, IL-8, AR, and PSA. These activities account for the suppression of angiogenesis by this stilbene. Resveratrol has also been shown to potentiate the apoptotic effects of cytokines (e.g., TRAIL, tumor necrosis factor-related apoptosis-inducing ligand), chemotherapeutic agents and  $\gamma$ -radiation. Pharmacokinetic studies revealed that the target organs of RSV are liver and kidney, where it is concentrated after absorption and is mainly converted to a sulfated form and a glucuronide conjugate. *In vivo*, RSV blocks the multistep process of carcinogenesis at various stages: it blocks carcinogen activation by inhibiting aryl hydrocarbon-induced CYP1A1 expression and activity, and suppresses tumor initiation, promotion, and progression.

Besides chemopreventive effects, RSV appears to exhibit therapeutic effects against cancer. Limited data in humans have revealed that RSV is pharmacologically quite safe. RSV acts as sensitizer of tumour cells to other inducers of apoptosis. RSV has no influence on normal human fibroblasts to TRAIL-induced apoptosis, but it has been shown that it sensitizes several tumour lines (77).

### *Inhibition of cyclooxygenase and ornithine decarboxylase*

There is epidemiological evidence that long term COX inhibition may reduce the risk of developing of many cancers (78). In a mouse model of colorectal cancer, deletion of the gene encoding COX2 was shown to be protective (79). *In vivo* RSV reduces the total COX activity of tumours and normal tissue via moderately selective inhibition of COX1 activity and/or reduction of COX2 at the mRNA level. *In vitro* studies indicate that transcriptional inhibition of COX2, as well as ornithine decarboxylase (ODC), could be accomplished through inhibition of PKC (10). Resveratrol does not directly inhibit ODC activity (80), but reduces its expression *in vivo* and prevents its induction by carcinogens.

### *Inhibition of angiogenesis*

In order to grow, tumors induce angiogenesis by secreting various growth factors like VEGF and are aided by enzymes called matrix metalloproteinases (MMP). RSV was shown to

inhibit tumor-induced neovascularization *in vitro* and *ex vivo* inhibiting the activities of MMP-2 (81) and the expression of MMP-9 (82). Both COX and ODC promote angiogenesis and their suppression by RSV could have an additional role.

### EFFECTS ON DRUG METABOLISM

Resveratrol modulates the expression and activity of different drug-metabolizing enzymes suggesting that it could cause a reduction in the exposure of cells to carcinogens. Resveratrol and its metabolites inhibit the enzymatic activity of phase I enzymes - various cytochromes P450 (CYPs) *in vitro*: CYP2C19, CYP3A4; CYP3A, CYP1A, CYP2E1 (83,84). However this could interfere with the pharmacokinetics of other drugs. Other papers showed RSV's capability of increasing the body's capacity to eliminate harmful molecules by inducing phase II conjugating and antioxidant enzymes (85,86).

### PHYTOESTROGENIC ACTIVITY

On the basis of the structural similarity of RSV to the synthetic estrogen diethylstilbestrol it was hypothesized and proved that RSV is a phytoestrogen and thus an agonist for the estrogen receptor (ER) (87). Resveratrol was able to elicit a dose-dependent activation of a luciferase reporter gene under the control of an estrogen response element (ERE) linked to the minimal thymidine kinase promoter in MCF-7 cells, an ER-containing human adenocarcinoma breast cell line. In this cell line, RSV produces a greater maximal transcriptional response than ER, whereas in others it produces activation equal to or less than that of ER. Suboptimal doses of RSV and estrogen were additive. Upon binding ER, RSV activates transcription of estrogen-responsive reporter genes. However, other studies showed that RSV acts as a possible mixed agonist/antagonist, depending on the availability of specific ER isoform (88), possesses antiestrogen activity (89) or super- or anti-estrogenic activity, depending on the concentration (90). Most of the *in vivo* studies failed to reveal estrogenic potential of RSV except a study on stroke-prone spontaneously hypertensive rats, demonstrating a decrease in the systolic blood pressure by 15% and stimulation of endothelium-dependent vascular relaxation in response to acetylcholine in ovariectomized rats (91).

### RESVERATROL AND LONGEVITY

Since the 1930s calorie restriction (CR) is known to extend the lifespan of a number of species, including mammals and nonhuman primates (92, 93). In the yeast *Saccharomyces cerevisiae*, CR extends lifespan by increasing the activity of

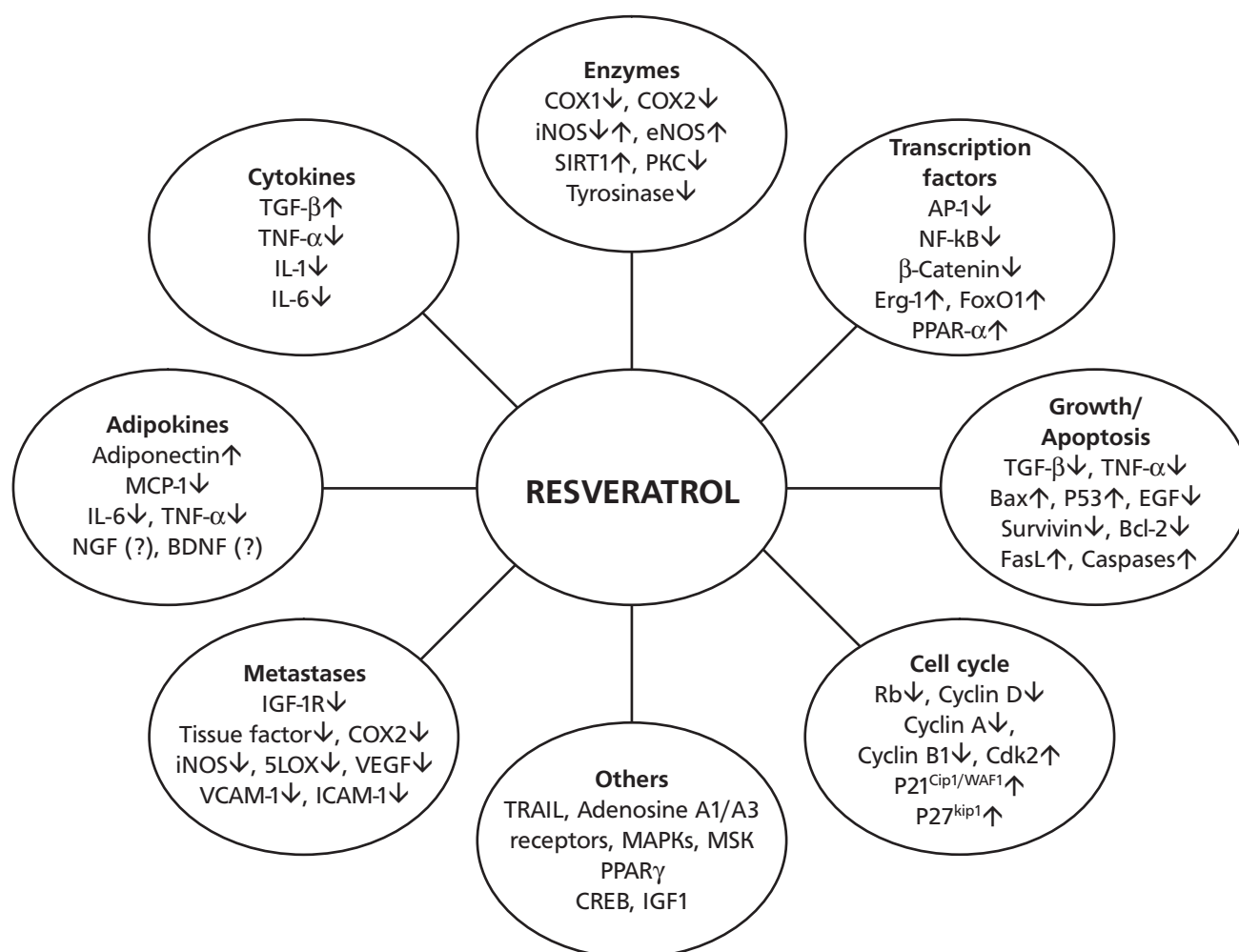
Sir2 enzymes (94). In yeast, worms and flies, overexpression of the genes encoding sirtuins are reported to extend lifespan (95-96), suggesting that sirtuins are evolutionarily conserved mediators of longevity, also called anti-senescent proteins. Sirtuins are a unique class of NAD(+)-dependent deacetylases, found in both prokaryotes and eukaryotes, and required for diverse biological processes. Sir2 is short for the gene *Silent (mating type) Information Regulator-2* of *Saccharomyces cerevisiae*. Of the seven mammalian sirtuins (SIRT1-7), SIRT1 is the closest homologue to SIRT2. While RSV is now a well-recognized activator of sirtuins, nicotinamide is an inhibitor of their enzymatic activity. Note that valproic acid, a common drug for therapy of epilepsy and depression, is also a deacetylase inhibitor, that inhibits adiponectin production (97), an action that may contribute to metabolic side effect of this drug.

Indeed, in the absence of CR, RSV has been found to be the most potent activator of SIRT1 out of 18 molecules after *in vitro* screening – it increased Sir2 activity in yeast and extended its replicative lifespan by 70% (98). By a similar mechanism RSV extended the lifespan of worms (*C. elegans*) and fruit flies (*D. melanogaster*) (99) and was also found to increase dose-dependently the lifespan of a vertebrate fish (*N. furzeri*) (100) and of mice on a high calorie diet, thus mimicking CR (101). Calorie restriction induces a shedding of body fat from white adipose tissue and an increase in insulin sensitivity. White adipose tissue appears to be a primary factor in longevity, as fat-specific insulin receptor knockout (FIRKO) mice live longer (102). At present, CR, though much promising in animal studies, doesn't seem to be an attractive way for humans – for just a 6-month proof of its benefits only 48 participants were found (103). Further searching for CR mimetics, including RSV and its analogues, appears a novel alternative in the field. Adipogenesis is promoted by the nuclear receptor peroxisome proliferator-activated receptor-gamma (PPAR- $\gamma$ ). Thiazolidinedione antidiabetic drugs are agonist ligands for PPAR $\gamma$  and thus insulin sensitizers. RSV has also been shown to be a PPAR- $\gamma$  ligand. Activating SIRT1, RSV attenuated adipogenesis by repressing PPAR- $\gamma$  activity what lead to fat mobilization in white adipocytes and to triggering of lipolysis (104). Resveratrol may additionally modulate lifespan through inhibition of insulin signaling pathway independently of SIRT1 activation by inhibiting insulin-induced MAPK and Akt (105). And last but not least, activating SIRT1, RSV increased the adiponectin levels in 3T3-L1 adipocytes (106). Reduced circulating levels of adiponectin usually accompany obesity,

diabetes, and atherosclerosis. All these data outline RSV as an important playmaker in cardiometabolic diseases and with a possible role in achieving longevity. It is not known whether RSV can extend human lifespan. Clinical trials in humans are underway, one phase I study already completed (107), which will provide information on safety and efficacy of RSV given in high doses as a dietary supplement.

Resveratrol is a molecule with many targets (108) (Fig. 2). The (xeno)hormesis hypothesis may in part explain such a pleiotropic potential of this wine-derived molecule (109). Calorie restriction, considered as mild stress, is a form of hormesis. Individuals (animals and possibly humans) that are mildly stressed, outlive their unstressed counterparts (10). Sirtuins evolved early in life's history to increase somatic maintenance and survival during times of adversity.

The hormesis hypothesis proposes that primordial species synthesized polyphenolic molecules to stimulate sirtuins during times of stress. Plants have retained this ability. Nevertheless animals and fungi have lost their ability to synthesize polyphenols, they have retained the ability to respond to plant stress signaling molecules. This ability would allow organisms to prepare for and survive adversity (109). If the xenohormesis hypothesis is correct, then stressed plants might form an abundant reservoir for medicinal compounds that trigger conserved protective responses in humans. There are numerous potential hormetics in a stressed plant that could act additively or even synergistically. Another potentially hormetic compound, quercetin (also a red wine compound), behaves similarly to RSV in many assays (110).



**Figure 2.** Molecular targets of resveratrol.

## CONCLUSION

Resveratrol is a pluripotent molecule with numerous beneficial effects, established in over 2000 studies (according Medline/Pubmed information), thus making it the (present) king of red wine. Resveratrol is also a two-faced molecule, since it can protect healthy cells and selectively kill cancer cells; it behaves as an antioxidant, yet it can induce redox signaling; it induces apoptosis in tumor cells and blocks apoptosis in ischemic heart (59). Despite low bioavailability, low concentration of RSV is quite sufficient for the preconditioning of the heart. Red wine containing 1.2 mg/l of RSV can inhibit platelet aggregation by 42%, even when it is diluted 100-fold (40). Preconditioning is the best method yet devised for cardioprotection, and RSV appears to fulfill the definition of a pharmaceutical preconditioning compound.

But shall we trust the nature and enjoy 2-4 glasses of good red wine a day and/or reach out for RSV capsules or even powerful analogues? There is sufficient evidence that wine has protective effect beyond alcohol, and that red wine is more useful than white wine regarding cardiometabolic biology (39). Among the reds remains the international debate, including Italy, France, Spain and soon Bulgaria to be involved, and the preference of Pinot Noir to Cabernet or Burgundy. Another important consideration is that beside RSV red wine contains other useful compounds like flavan-3-ols (catechins, procyanidins), flavonols (quercetin) and anthocyanins (cyanidin, delphinidin). The high content of red wine procyanidins may be essential to cardiovascular health (111).

One should be very cautious concerning transition of scientific data into everyday life. There is no standing rule how to estimate RSV daily dosage for humans from that given, for example, to a mouse. Is the sight of extended human lifespan real or it is only too much fuss because of commercial interests in creating antiageing drugs? Behind the names of renown scientists show through the names of companies like Sirtris Pharmaceuticals (for Longevinex, RSV in pills, see [www.longvinex.com](http://www.longvinex.com)) and Elixir Pharmaceuticals. Some other groups (112) could not reproduce the results of Sinclair *et al*, and even the ability of RSV to activate sirtuins has been questioned (113,114). Optimistically, sirtuins were included in the list of endogenous metabotropic factors (115) and a recent study demonstrated that small molecules that are much more potent in activating sirtuins than RSV itself could exert anti-diabetic effect (116). Nevertheless, while the discussion is still hot and the probable role of sirtuin activators is still being elucidated let us rely on nature's gifts and hope that a

glass of red wine each day will keep cardiometabolic disease at bay.

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